REMARKS

Reconsideration and withdrawal of the rejections of the pending claims and consideration and entry of this paper are respectfully requested in view of the amendments and remarks herein, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 3-11, 13, and 14 are pending in this application. Claims 13 and 14 have been amended. Claim 13 has been amended to recite elected subject matter, and claim 14 has been amended for clarity. No new matter has been introduced.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. It is submitted that the amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

Applicants note with appreciation that the Examiner has granted Applicants' traversal of the restriction requirement in part and that Group IV (claims 13 and 14, in part) have been examined with Group I.

Applicants also note with appreciation that the § 112 rejections have been withdrawn.

The issues raised by the Examiner in the Office Action are addressed below in the order they appear in the prior Action.

II. THE REJECTIONS UNDER 35 U.S.C. § 103 ARE OVERCOME

Claims 1 and 3-12 are rejected under 35 U.S.C. § 103(a) as being obvious over Nicolaou et al. (*Agnew. Chem. Int. Ed. 1998, 2014-2045*, hereinafter "Nicolaou") in view of Patani et al. (*Chem. Rev. 1996, 3147-3176*, hereinafter "Patani"). Applicants respectfully traverse. The cited references do not render the pending claims obvious.

The Examiner asserts that Patani teaches that a carbonyl group can be replaced by SO and that the change has been used increasingly in the pharmaceutical art. The Examiner further alleges that Nicolaou teaches epothilones with a carbonyl rather than a sulfoxide group at the C5

position of the epothilone ring and that it would have been obvious to one of skill in the art to follow the synthetic scheme of Nicolaou with the replacement of Patani. The Examiner contends that the motivation to do so is provided by Nicolaou because Nicolaou allegedly teaches the use of such compounds as killers of tumor cells.

Applicants submit herein a table, attached as Exhibit A, summarizing biological data, which demonstrates that replacement of the carbonyl moiety at the 5-position with SO results in epothilone derivatives with a similar or better range of activity against certain cancer cell lines, in particular cell lines MCF-7 and KB-31.

Patani discusses at column 1, page 3167, a series of benzophenone dicarboxylic acids as potential inhibitors of LTB_4. Further, the sulfones depicted in Table 39 show a similar activity in comparison to the carbonyl derivatives. Based on these results, Patani concludes that this portion of the molecule is not critically involved in LTB_4 receptor binding. Further, at column 2, page 3167, Patani contends that the greater size associated with the sulfone moiety has been shown to be a factor that modulates biological activity. As such, Patani teaches that if CO is replaced by SO in a non-critical part of a molecule, one skilled in the art would expect no significant change in the biological activity of the molecule. On the other hand, if CO is replaced by SO in a part of a molecule that is relevant for biological activity, Patani would expect major changes in the biological activity of the compound.

Nicolaou at page 2040 discusses that a loss of activity was observed when the C5 ketone was reduced or when the C5 substituent was removed. As such, Nicolaou clearly shows that the CO moiety at the C5 position is of great importance for the activity of epothilone derivatives. In this regard, one skilled in the art would expect that replacing CO with SO at C5 of an epothilone derivative would have a significant influence on the biological activity of the compound. Thus, one of ordinary skill in the art would not expect the biological activities that have been demonstrated for compounds of the instant claims.

In addition, the angle between the two R groups in an R-CO-R molecule is 120° whereas the angle between the two R groups in an R-SO-R molecule is less than 100°. Further, since the sulfone moiety is of a greater size than the ketone moiety, one skilled in the art would expect that replacement of CO by SO would have a significant influence on the conformation of a macrocycle and therefore, the skilled artisan would expect that this also would have a significant

influence on the biological activity of the corresponding derivative. As shown in Exhibit A, this is not the case for epothilone derivatives of the pending claims.

Furthermore, in an R-CO-R molecule, all groups lie within one plane whereas in an R-SO-R molecule, the oxygen is positioned either above or below the plane created by the R-S-R group. Therefore, one skilled in the art would expect that the activity of an epothilone derivative, wherein the CO moiety at position C5 is replaced by a SO moiety, would be comparable with the activity of a derivative carrying an OH group at C5. As discussed above, Nicolaou teaches that this derivative shows a loss of activity.

For the foregoing reasons, the references cited by the Examiner do not render the claimed subject matter *prima facie* obvious under 35 U.S.C. § 103(a). Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

III. THE PROVISIONAL DOUBLE PATENTING REJECTION IS OVERCOME

Claims 1 and 3-12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12 and 22 of copending Application No. 10/535,474 in view of Patani.

Applicants reiterate that the issue of whether there is indeed double patenting is contingent upon whether the instant claims herewith are indeed considered and, if so, whether the Examiner believes there is overlap with the claims ultimately allowed in the instant application and co-pending Application No. 10/535,474. If, upon agreement as to allowable subject matter, it is believed that there is still a double patenting issue, a Terminal Disclaimer as to Application No. 10/535,474 will be considered.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

IV. THE OBJECTIONS TO THE CLAIMS ARE OVERCOME

Claims 13 and 14 are objected to for containing elected and non-elected subject matter. In order to expedite prosecution of the pending claims, claims 13 and 14 have been amended to recite the elected compounds. Accordingly, the objections to the claims are obviated.

V. THE REJECTIONS UNDER 35 U.S.C. § 101 ARE OVERCOME

Claim 14 is rejected under 35 U.S.C. § 101 because the claimed recitation of a use allegedly results in an improper definition of a process. Applicants respectfully traverse with respect to the claim as amended.

As amended, claim 14 recites a process for preparing a compound of formula (I), comprising reacting a compound of formula (Va) or (Vb) according to the recited reactions.

Accordingly, reconsideration and withdrawal of the § 101 rejection is respectfully requested.

VI. THE REJECTIONS UNDER 35 U.S.C. § 112 ARE OVERCOME

Claim 14 is rejected under 35 U.S.C. § 112, second paragraph as allegedly being unclear as to what method or process is encompassed. Applicants respectfully traverse with respect to the claim as amended.

As discussed above, claim 14 as amended recites a process for preparing a compound of formula (I), comprising reacting a compound of formula (Va) or (Vb) as indicated.

Accordingly, reconsideration and withdrawal of the § 112 rejection is respectfully requested.

CONCLUSION

In view of the foregoing remarks, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

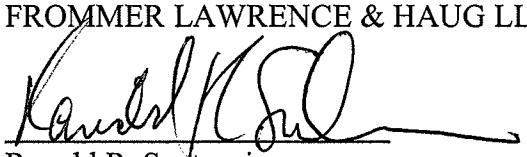
By: 

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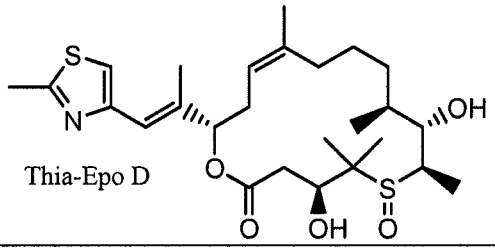
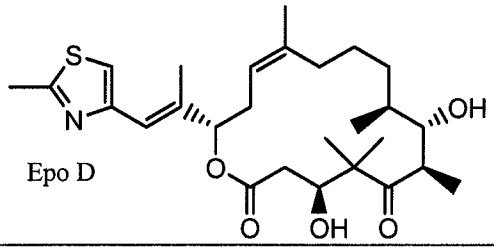
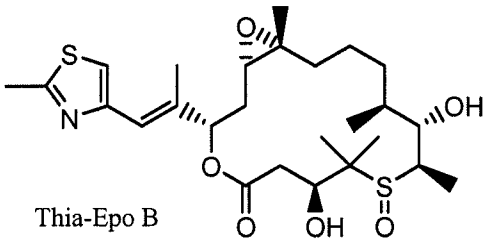
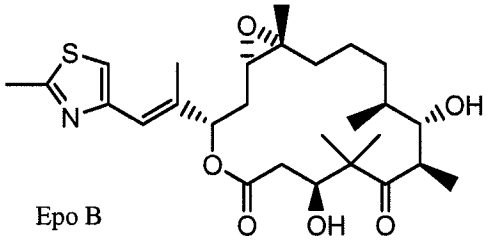
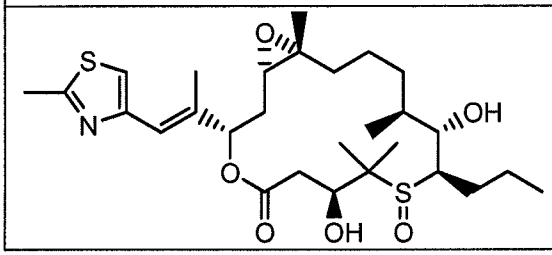
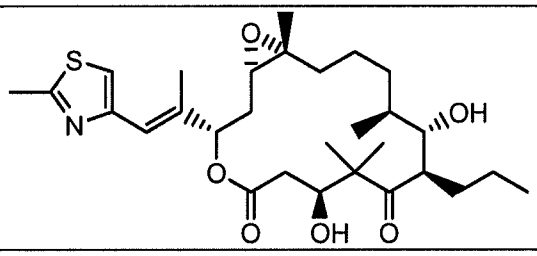
EXHIBIT A

Epothilone with SO at 5-position	IC_{50} (nM)	Epothilone with CO at 5-position	IC_{50} (nM)
Thia-Epo D 	1.1-3.0 MCF-7	Epo D 	2-5 MCF-7
Thia-Epo B 	0.1-0.2 MCF-7 0.4-1.5 KB-31	Epo B (Altmann, K.-H., Mini Rev. in Med. Chem., 2003, 3:149-158) 	0.42 MCF-7 0.19-1.2 KB-31
	0.2-0.9 MCF-7		0.5-1.0 MCF-7